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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,613	01/30/2006	Richard G Vile	07039-444US1	6311

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/533,613	VILE ET AL.	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/30/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims **1-22** are pending and presently under examination.

Specification

Priority

Applicant's claim for the benefit of priority to PCT/US03/34599 with the date of filing 10/31/2003 has been granted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims *1-22 are* rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses any and all viral vectors comprising a nucleic acid encoding a therapeutic peptide for treating any and/or all diseases wherein said nucleic acid is operably linked to any and/or all heterologous destabilizing elements, administration of the vector into any target cell of any organism under any condition (in vivo, ex-vivo or in vitro) wherein it causes an enhanced expression of the therapeutic polypeptide relative to non-target cells and further encompasses a methods of treating any and/or all tumors by administering said viral vectors to a subject by any routes of administration.

At best the specification teaches an adenoviral vector with a E1A protein coding sequences that is operably linked to a sequence encoding 3' UTR of cyclooxygenase-2 mRNA (Ad-E1A-COX), wherein the vector when introduced into target cells expressing

RAS protein exhibit an enhanced stabilization and translation of the transcripts of said therapeutic coding sequences relative to cells that do not express RAS protein. The specification further teaches treating tumor by administering said vectors by direct injection into an experimental tumor implanted in rats and nude mice.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see <http://www.uspto.gov>). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e conserve motifs or domains).

. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the limited disclosures in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within

its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the nucleic acid sequences as claimed has been defined only by a statement of function that broadly encompasses all destabilizing sequences of an mRNA transcript which conveyed no distinguishing information about the identity of the claimed genetic material, such as its relevant structural or physical characteristics. According to these facts, one skilled in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this genus would not be representative of other nucleic acid constructs genus and is insufficient to support the claim.

Claims 17-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a glioma in an experimental animal with an oncolytic adenoviral vector with a E1A protein coding sequences that is operably linked to a sequence encoding 3' UTR of cyclooxygenase-2 mRNA, wherein said vector was introduced by direct injection to the site of tumor, does not enable treatment of any tumors, in any subjects using any viral vector with any therapeutic peptide coding sequences with stretch of any heterologously derived conditionally destabilizing sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Since the specification fails to disclose treatment of a tumor with any other viral vectors of said nature other than one described above, it is unclear how one skilled in the art use the invention as claimed (supra). The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation, which requires the identification and characterization of any and all heterologous destabilizing sequences and the conditions under which they do so. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether,

given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention and the breadth of the claims: The scope of the invention as claimed encompasses treatment of any and all tumors with any and all viral vectors comprising nucleic acids encoding any/and all therapeutic peptides and operably linked to any conditional mRNA destabilizing heterologous elements including certain 3' UTR elements from tumor necrosis factor alpha gene, cyclooxygenase-2 gene, vascular endothelial growth factor gene, urokinase plasminogen activator receptor gene etc., and administering said vectors by any route to a subject. In the absence of representative number of enabled examples in the specification commensurate with the breadth of the claims one of ordinary skill in the art would conclude that the invention is unpredictable and would require undue experimentation to practice the invention in its full scope. Applicants' attention is drawn to In re Shokal, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the number of claimed genus/or species of expression vectors, sites of administration to a subject, and cardiac diseases whose treatments are successfully completed by applicants prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is

high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

Guidance of the Specification and the Existence of Working Examples: Applicant's examples demonstrate the making and using of a recombinant adenovirus vector with E1A coding sequence fused with cyclo-oxygenase-2 3'UTR sequence (Ad-E1A-COX) and driven by a cytomegalovirus (CMV) immediate early gene promoter-enhancer and testing of the same in tumor cell lines for its efficacy in killing tumor cells. The above vector is further delivered by injection into subcutaneous tumors established in rats using U118 human glioma cell line. The oncolytic property of said vector administered directly by injection into said tumors was superior to control vectors lacking destabilizing COX-2 sequences and over that was administered systemically. However, given the lack of reasonable predictability in the art, even in the face of Applicant's disclosure, the Artisan would not reasonably predict that any vector could be used, that any tumor tissue could be treated. Given the state of the art coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods of treating all heart diseases as claimed.

State of the Art, the Predictability of the Art: Art is still unpredictable with regard to efficacy, specificity and safety. Hence, the Artisan, before, and even after the date of invention, recognized that the type of vector was critical to the invention and demonstration of any single vector would not reasonably predict the use of any other vector. Gene therapy or in vivo gene transfers are still considered to be highly experimental area of research and it has been difficult to predict the out come of many therapeutic genes and vector systems because of various factors that govern the expression, therapeutic potential of the transduced genes, and the undesirable host immune reactions etc., in vivo (Reviewed in Goncalves et al, Bioessays, 2005, 27: 506-517). In addition there exists an unpredictability about the degree to which a foreign gene or vector would interfere with cellular genetic material as observed in treatment of X-SCID patients " These serious adverse events presented as a leukemia-like

syndrome were surprising since the risk of insertional oncogenesis was considered to be negligible based on previous trials and on the perceived, though not universally accepted, notion of random retroviral integration" (Goncalves, Bioessays, 2005, 27: 506-517, p. 514, col.2, 1st ¶). Curiel et al (2000, Clinical Cancer. Res. 6:3395-3399). teaches obstacles for clinical application of conditionally replicative adenoviruses in treating tumors because of the scarcity of adenoviral receptors on human tumors for specific targeting and because of the observed adverse interactions adenoviral vectors with immune system (p.3397, col.2, 2nd paragraph bridging p. 3398, col.1). Because of the uncertainties expressed art regarding use of viral vectors as shown above, Artisan could not predict, in the absence of proof to the contrary, that such applications of any and/ or all viral vectors as claimed would be efficacious and safe in any gene therapy treatment of any tumor. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as broadly claimed by Applicant is not enabled.

Amount of experimentation necessary: Because of the lack of sufficient number of working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability of the art, and the nature of the invention, one of skill in the art would be required to perform a large amount of experimentation to make and/or use the invention in its full scope as claimed by Applicant. Such experimentation would be required to determine the types of vectors that could be used, the tissues tumors that could be treated, and the types of promoters that would produce enough protein for a long enough period of time to effect safe treatment. Further these claims are not enabled because one of skilled in the art, at the date of filing, would not be able to rely upon the state of the art in order to successfully predict a priori the in vivo effects of claimed gene transfers in a subject. Accordingly, in view of the lack of teachings in the art or guidance provided by the specification with regard to an enabled use of a method for safe treatment of a any and/or all tissue tumors by genetherapy, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the best the specification as filed is found only enabled for a method of gene therapy for treating treating a glioma in with an oncolytic adenoviral

vector with a E1A protein coding sequences that is operably linked to a sequence encoding 3' UTR of cyclooxygenase-2 mRNA, wherein said vector was introduced by direct injection to the site of tumor.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 9, 10 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by *WO 98/5936 published 12/171998*.

The above claims are directed to a viral vector comprising a therapeutic polypeptide coding sequence that is operably linked to a heterologous destabilizing element that enhances the expression of said polypeptide in target cells including tumor cells

Regarding claims 1, 2, 9 and 10 WO 98/5936 teaches compositions of recombinant viral vectors including adenoviral and retroviral vectors for gene therapy of tumors etc., (abstract, p.1, and p.18, 2nd paragraph) comprising therapeutic polypeptide coding sequences (p.11, 2nd paragraph bridging p.12, 1-2ndparagrph) with heterologous regulatory sequences derived from 3' untranslated region of vascular endothelial growth factor (VEGF) gene (abstract, p.1 and entire document) and wherein which said regulatory sequences are involved in hypoxia- regulated modulation (expression) of the therapeutic gene in target cells (p.5, 2nd paragraph). Regarding claim 22 *WO 98/5936* teaches hypoxia-mediated expression of the cloned genes with said regulatory elements in tumors of syngenic Fischer 344 rats (p.34, 2nd paragraph).

Rejected claims are within the scope of *WO 98/5936*'s disclosure.

Claims 1, 2, 9, 10, and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by *Boast et al (1999, Human gene Therapy 10:2197-2208)*.

The above claims are directed to a viral vector comprising a therapeutic polypeptide coding sequence that is operably linked to a heterologous destabilizing element that enhances the expression of said polypeptide in target cells including tumor cells

Regarding claims 1, 2, 9 and 10 Boast teaches construction of a recombinant vectors including a retroviral vector for gene therapy of a broad range diseases ischemic pathology including tumors etc., (abstract, p.1, and p.2197, summary, 2206, col.1, 2nd paragraph) wherein which inclusion of a hypoxia response element (HRE) operably linked to a heterologous gene of therapeutic value allows the inducible expression of the gene under hypoxic conditions. Regarding claims 12-13 Boast teaches the use of retroviral vectors based on Moloney murine leukemia virus (MLV) which are conditionally replication comptent in being able to infect and grow strictly in rapidly dividing cells (p.2197, col.2 bridging p.2198, p. 2206, col.1, 2nd paragraph).

Rejected claims are within the scope of *Boast*"s disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-8, 12-15, 17-19 are rejected under 35 USC 103 (a) as being unpatentable over *WO 98/5936*, as applied to claims 1, 2, 9, 10 and 22 as above in view of Sheng et al (2000, J. Biol. Chem. 275:6628-6635) and Curiel et al (2000, Clinical Cancer. Res. 6:3395-3399).

The above claims are directed to a viral vector comprising a therapeutic polypeptide coding sequence that is operably linked to a heterologous destabilizing element that enhances the expression of said polypeptide in target cells including tumor cells

Regarding claims 1, 2, 9 and 10 WO 98/5936 teaches compositions of recombinant viral vectors including adenoviral and retroviral vectors for gene therapy of tumors etc., (abstract, p.1, and p.18, 2nd paragraph) comprising therapeutic polypeptide coding sequences (p.11, 2nd paragraph bridging p.12, 1-2ndparagrph) with heterologous regulatory sequences derived from 3' untranslated region of vascular endothelial growth factor (VEGF) gene (abstract, p.1 and entire document) and wherein which said regulatory sequences are involved in hypoxia- regulated modulation (expression) of the therapeutic gene in target cells (p.5, 2nd paragraph). Regarding claim 22 *WO 98/5936* teaches hypoxia-mediated expression of the cloned genes with said regulatory elements in tumors of syngenic Fischer 344 rats (p.34, 2nd paragraph). However, *WO 98/5936* does not teach cyclooxygenase-2 gene 3' UTR sequences as destabilizing elements, its stabilization in proliferating cells or its reposiveness to RAS and P-MAPK activity and conditionally replicative Adenovirus.

Sheng teaches regarding claim 6-8 of the use of 3'UTR sequences of cyclooxygenase-2 and regulation of gene expression in vector constructs where in which said sequences are operably included (abstract, p.6629, col.1-2). Sheng further teaches that inclusion of COX-2 3' UTR sequences in said constructs cause stabilization and induction of the heterologous gene (luciferase gene) in H-Ras induced cells (p.6631 col.1-2). Art teaches Ras oncogene is induced in proliferating cells for example cancer cells (p.6634, col.3 and 3 rd paragraph).

Curiel teaches regarding claim 12-15, 18-19 the development of a conditionally replicative Adenovirus for cancer therapy (p.3395, abstract). Curiel further teaches engineering of specificity conditionality of replication is based on tumor biology, based on transcriptional control especially of E1A gene in various cancer cells (p.3396-97)

Thus it would have been obvious for one of ordinary skill in the art to operably incorporate into compositions of therapeutic gene constructs in conditionally replicative

Adenoviral vectors with E1A gene under 3'UTR conditional mRNA stabilizing elements for treating tumors. One skilled in the art would be motivated to do so as the 3'UTR elements selectively stabilize and enhance therapeutic (eg.oncolytic) genes or viruses in cancer cells that express RAS gene and use of conditionally replicative virus adds to safety of the vector and thereby safely and selectively killing cancer cells. One of ordinary skill in the art would have reasonable expectation of success of using the viral vectors incorporating said 3'UTR elements for treating tumor because of the teachings of *WO 98/5936 and* Sheng and Curiel as above. Thus, the claimed invention was *prima facie* obvious.

Note: Other 102 references considered but not cited include Schwartz et al (U.S.Patent No.:5,925,564); Knirsch et al (2000, BBRC 272:164-168); Gale et al., (2000, microbiology and Molecular Biology Reviews 64:239-280).

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at **(571) 272-0731.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is

available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

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